Correlations of Chemical Mass Shifts of *para*-Substituted Acetophenones and Benzophenones with Brown's σ_p^+ Constants

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Relationships between chemical mass shifts and physiochemical properties of ions are sought by examining substituted acetophenones, benzophenones, and pyridines in a modified ion trap mass spectrometer. Systematic changes in chemical mass shift occur with changes in substituent in the acetophenones and the benzophenones. Brown's σ^+ constant, which is a measure of electronic effects of substituents in reactions that involve positive charge development, is shown to correlate linearly with chemical mass shifts in *para*-substituted acetophenones and benzophenones. Brown's σ^+ constant also correlates with the ease of dissociation of the ions via a correlation with ionization energy. It is suggested that ease of dissociation is the underlying factor in determining chemical mass shifts. The experimental results also suggest that dissociative collisions between ions and buffer gas make a much greater contribution to chemical mass shifts than do elastic collisions. (J Am Soc Mass Spectrom 2002, 13, 623–629)

The quadrupole ion trap is a radio-frequency device invented by Wolfgang Paul in 1953 [1]. Since the introduction of the mass-selective instability scan by Stafford et al. in 1984 [2], ion traps have been used successfully as mass analyzers and found a wide variety of applications in analytical, environmental, and biochemical studies. The modern ion trap mass spectrometer offers high sensitivity, high mass resolution, and access to high mass ions, it is compatible with various ionization methods and has multi-stage tandem mass spectrometry capabilities. Despite these advantages, the mass measurement accuracy is still limited. Most commercial instruments have a mass accuracy of ±0.1 Dalton/charge, although 10 ppm accuracy has been reported [3]. The poor mass accuracy is due to a combination of several factors including the stability of RF voltage, buffer gas pressure, and space charge effects. Enhancement in the performance and applicability of quadrupole ion trap mass spectrometers has been sought through variation of the physical structure of the device and changes in operating parameters [4–7]. Improvements in mass accuracy might also be available through a thorough study and understanding of the phenomenon of chemical mass shifts.

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Chemical mass shifts were first observed during the early development of commercial ion trap instruments. For some ions, Stafford and coworkers observed errors in *m/z* as large as 0.7 Th (1 thomson = 1 Da/charge [8]), even under experimental conditions where the measured *m/z* was in good agreement with the true *m/z* for other ions. These compound-specific chemical mass shifts can be eliminated empirically by adjusting the electric field in the ion trap, for example by increasing the distance from the center of the trap to the end-cap electrode z_0 from theoretical value 0.707 cm to 0.783 cm. (The theoretical value of z_0 is the value that corresponds to a pure quadrupole geometry using the relationship $r_0^2 = 2z_0^2$ for a ring electrode diameter $r_0 = 1.0$ cm.) In the stretched geometry, the value of z_0 is increased by 10.6% without any corresponding modification to the hyperbolic shape of the ring electrode which would be required to maintain a pure quadrupole field, thereby adding higher-order field contributions to the overall trapping field [9]. These higher-order field contributions due to alteration in the geometry of the trap offset the field imperfections caused by end-cap holes and electrode truncation. Note that the existence of end-cap holes distorts the pure quadrupole field and causes *local* field faults that result in the addition of negative higher-order fields in this region. On the other hand, increasing the end-cap distance introduces a *global* positive higher-order field. At the appropriate stretched geometry these two different kinds of higher-order fields approximately cancel, which eliminates the chemical mass shift. Today, all commercial ion trap mass

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spectrometers employ a stretched or otherwise altered geometry so that chemical mass shifts are almost completely removed.

Although chemical mass shifts can be successfully eliminated by changing z_0, their origin and nature remain an interesting topic that has been studied by several research groups [10–17]. This interest is sustained by the possibility that chemical mass shift measurements might have analytical significance. In addition to ion trap geometry, ion polarizability, dipole moment and the radial distribution of the ion population have each been suggested as factors that influence the magnitude of chemical mass shifts [10–17]. Fragmentation has been suggested by March and coworkers as a possible cause of the chemical shift [14], and Yost et al. have provided experimental evidence that ions which show mass shifts have undergone dissociation during ejection [18]. Our group reached the same conclusion using a combination of experiment and simulation to show that chemical mass shifts are associated with delays in ion ejection due to field faults. Fragmentation modifies these delays and so influences chemical mass shifts [19–21].

The way in which the propensity for dissociation causes changes in mass shifts has been explained [19, 22] using the multi-particle ion trap simulation program ITSIM [23, 24] which allows a large number of ions to be studied and provides realistic mass and kinetic energy data. The program was modified for the chemical mass shift study to allow a detailed examination of the change in geometry and other experimental variables on the ejection profile of a collection of ions of interest [21]. In the new version of the ITSIM program, the electric field in the ion trap can be calculated separately using Poisson/Superfish software [25]. This allows the consideration of local field effects caused by the inclusion of end-cap holes.

In an ideal ion trap with a pure quadrupole field, the electric field varies linearly from the center of the trap to the end-cap electrode and then abruptly reaches zero. However, the end-cap holes in a real ion trap lead to the non-linearity in the electric field along the axial direction just discussed. A slower than quadratic field increase in the vicinity of the end-cap electrodes, corresponding to negative higher-order field components, is associated with field penetration into the end-cap apertures. Therefore, the ions experience a smaller increase in field strength at positions close to the end-cap electrodes than a quadrupole field would provide. During rf ramping to perform a mass-selective instability mass scan, ions become unstable at the boundary of the Mathieu stability diagram, viz. at $q_z = 0.908$ [22, 26], and within a few cycles of the trapping field begin to be ejected from the trap. In the course of ejection, the ions enter the region of weakened field near the end-caps where their motion is stable—they are no longer accelerated from the trap and with collisions their excursions decrease. The ions then experience the higher field with larger gradient near the trap center, become unstable, and their oscillation amplitudes again increase. The whole sequence occurs repetitively and causes the delay in the ejection of the ions, relative to the ideal case of a theoretical geometry without end-cap holes. The ejection delay occurs for all ions, regardless of their masses or chemical structures. The fact that chemical mass shifts are compound-dependent is the result of differences in the interactions between the ions and the buffer gas during the ejection delay. Collision and fragmentation probabilities are different for different compounds and this leads to differences in ejection delay and hence different mass shifts. In summary, experiments and simulations indicate that chemical mass shifts are the result of the combination of two interacting factors: Ejection delay during the mass analysis scan due to field faults and compound-specific modifications of this delay by collisions with the buffer gas.

Wells et al. [19] showed that the size of the ions is a factor influencing chemical mass shifts in *n*-alkylbenzenes. However, many molecular ion properties change across this series of compounds including polarizability, dipole moment, charge transfer reactivity, propensity for dissociation, and number of degrees of freedom. Each of these factors may dependently or independently affect the magnitude of the chemical mass shift. In the present study we have selected a series of compounds in which aromatic substituents are changed in an attempt to isolate electronic effects on chemical mass shifts for study.

Hammett linear free energy relationships take the form $\log(k_X/k_H) = \rho\sigma$ where k_X and k_H are the reaction rates for a substituted compound and the unsubstituted compound, respectively, ρ is a constant for the particular reaction type and σ are the constants used to express substituent effects. This relationship has been widely applied in the study of solution phase reactions and their mechanisms [27]. Brown et al.[28] introduced a modified substituent constant σ^+ to treat *meta* and *para* substituent effects on the rates and equilibria of reactions that involve transition states in which positive charge accumulates in the reaction center. This equation has also been successful in treating electronic effects of substituents in a few mass spectrometric studies. For example, correlations have been shown between σ^+ values and ionization energies [29], and appearance energies [30], and with the degree of dissociation [31]. Substituent constants have also been correlated with reactivity, for example in the bromination of gaseous aromatic compounds using $BrCO^+$ [32].

The experiments were performed by systematically measuring chemical mass shifts for a series of substituted acetophenones, benzophenones, and pyridines in a modified Finnigan GCQ ion trap mass spectrometer. Plots of mass shifts against Brown's substituent constant σ^+ are used to test for electronic effects of substituents on chemical mass shifts.

Experiments

The experiments were performed using a modified Finnigan GCQ mass spectrometer (ThermoFinnigan Cooperation, San Jose, CA). The original commercial instrument has been modified in a number of ways to meet the requirements of the current study. Most significantly, instead of using the electrode spacers which fix the center-to-electrode distance at $z_0 = 0.783$ cm when the ring electrode has a radius of $r_0 = 1.0$ cm, a new set of spacers was used to change the value of z_0 to 0.707 cm while keeping the same size ring electrode. All experiments reported here were conducted using this geometry, i.e., a geometry containing large uncompensated higher-order fields.

Other important modifications were made to the instrument control and data acquisition systems. The commercial GCQ data acquisition hardware and software system was replaced by the control and acquisition module from a Finnigan LCQ mass spectrometer. The module kit includes an embedded 486 microprocessor with an Ethernet connection to a host Gateway 2000 PC. This LCQ system controls the digital signal processing and digital synthesizing board to generate reference signals for the RF and other waveforms, collect data from the detector, and change operational parameters by communication between the PC and the instrument. More significantly, this module allows the instrument to be controlled with Finnigan Ion Trap Control Language (ITCL), which provides much more versatility than the standard GCQ software.

The mass scale was calibrated using an ITCL procedure that directly calibrated the instrument using the fragment ions of *m/z* 69 and 131 generated from perfluorotributylamine (PFTBA). The measured mass values were obtained from the data system display by making the measurement at the maximum peak height and they were then compared to the exact theoretical monoisotopic mass values in order to calculate the mass shifts. For each data point, three measurements were made and the reported uncertainty of these measurements is taken as the range that includes all the data.

Samples were introduced by placing a small sample vial in a Cajon Ultratorr fitting (Cajon Co., Macedonia, OH) located at the head of a 20 m, 250 μm ID, deactivated column in the GC oven. The GC oven can be heated to 350 °C so that relatively non-volatile samples can be used. The sample vapor was carried into the ion source by helium, flowing at a constant rate of 20 cm s^{-1} through a heated transfer line at a fixed temperature of 250 °C. The ion source temperature was set at 200 °C. Electron ionization (EI) was used with Automatic Gain Control (AGC) to adjust the ionization time so that a constant number of ions were injected into the trap. By controlling the total number of ions in the trap, it is possible to minimize space charge effects. All chemical compounds are commercially available from Aldrich (Milwaukee, WI) and used without further purification.

Results and Discussion

In an effort to study the chemical factors that influence mass shifts, we chose *para*-substituted acetophenones to examine substituent effects systematically. There are several reasons of selecting this class of compounds as the subject of study. First, the individual compounds show large chemical mass shifts, allowing accurate comparisons of the differences in mass shifts within a set of compounds with different substituents. Acetophenone itself is reported to display a mass shift of 0.83 Th using the ideal trap geometry [19], i.e., the unstretched geometry of $z_0 = 0.707$ cm at $r_0 = 1.0$ cm. Secondly, previous studies suggested that both elastic collisions and inelastic collisions make contributions to chemical mass shifts [19]. Elastic collisions are expected to be size-dependent, so all the *para*-substituted acetophenones should have similar elastic scattering cross-sections since their molecular ions have similar physical sizes. This should facilitate investigation of the contributions of inelastic collisions. Finally, even within the same series of compounds, molecular ions can fragment very differently from one another. Our interest is to investigate the influence of one specific factor on chemical mass shifts; therefore simple, uniform fragmentation pathways within a given series of compounds can greatly simplify the study of substituent effects. For the p-acetophenones, the principal fragmentation pathway is that shown in eq 1, where *X* stands for the *para*-substituent:

$$XC_6H_4COCH_3^{\cdot +} \rightarrow XC_6H_4CO^+ \rightarrow XC_6H_4^+ \qquad (1)$$

To study substituent effects on chemical mass shifts, we measured the shifts for a series of p-acetophenones using an ion trap of ideal geometry, i.e., with large higher-order field contributions. The experimental data are tabulated in Table 1. In this table, monoisotopic mass refers to the exact ion mass. Apparent mass refers to the experimental result read from mass spectrum, after mass calibration. The reported mass shift is a relative mass shift and is defined as the mass difference between the monoisotopic mass and the apparent mass. Following a convention used in previous publications from our laboratory, a positive mass shift means that the apparent mass of the molecular ion is lower than the actual mass. Finally, the relative mass shift is corrected in order to minimize the *mass* dependence of chemical mass shifts. Simulation results show that heavier ions will travel more slowly inside the trap and thus be ejected later than lighter ions; therefore, the chemical mass shift increases with ion mass in an approximately linear fashion [21]. This mass dependence of chemical mass shift is of secondary interest and can be easily eliminated by the following correction (eq 2):

Table 1. Chemical Mass Shifts for *para*-Substitued Acetophenones and Benzophenones

	Monoisotopic mass	Apparent mass (uncertainty)	Relative mass shift (uncertainty)	Corrected relative mass shift (uncertainty)
H	120.06	119.32 (+0.01)	0.74 (±0.01)	0.74 (±0.01)
p-NH_2	135.07	134.24 (±0.02)	0.83 (±0.02)	0.63 (±0.02)
p-OH	136.05	135.21 (±0.01)	0.84 (±0.01)	0.67 (±0.01)
p-OCH_3	150.07	149.14 (±0.02)	0.92 (±0.02)	0.68 (±0.02)
p-CH_3	134.07	133.25 (±0.01)	0.83 (±0.01)	0.73 (±0.01)
p-$C(CH_3)_3$	176.12	175.03 (±0.01)	1.09 (±0.01)	0.75 (±0.01)
p-F	138.05	137.20 (±0.01)	0.85 (±0.01)	0.74 (±0.01)
p-Cl	154.02	153.07 (±0.02)	0.95 (±0.02)	0.76 (±0.02)
p-CN	145.05	144.16 (±0.01)	0.89 (±0.01)	0.79 (±0.01)
p-NO_2	165.04	164.03 (±0.02)	1.02 (±0.02)	0.80 (±0.02)
Benzophenones				
H	182.07	181.19 (±0.01)	0.88 (±0.01)	0.88 (±0.01)
p-NH_2	197.08	196.25 (±0.02)	0.83 (±0.02)	0.77 (±0.02)
p-OH	198.07	197.16 (±0.02)	0.91 (±0.02)	0.84 (±0.02)
p-OCH_3	212.08	211.14 (±0.02)	0.94 (±0.02)	0.81 (±0.02)
p-CH_3	196.09	195.13 (±0.02)	0.96 (±0.02)	0.89 (±0.02)
p-CF_3	250.06	248.76 (±0.01)	1.30 (±0.01)	0.95 (±0.01)
p-NO_2	227.06	225.86 (±0.01)	1.20 (±0.01)	0.96 (±0.01)

$$\textit{corrected relative mass shift} = \frac{(\textit{relative mass shift}) \times (\textit{mass of unsubstituted compound})}{\textit{mass of substututed compound}} \quad (2)$$

By plotting the corrected relative mass shifts of substituted acetophenones versus Brown's σ^+ constant, the substituent effect on chemical mass shifts can be examined. Figure 1 shows that a good correlation exists between the corrected relative mass shifts of *para*-substituted acetophenones and Brown's σ^+ constant. Acetophenone itself, $\sigma^+ = 0$, displays a corrected relative mass shift of 0.74 Th and aromatic substituents modify the magnitude of the mass shift for the substituted acetophenones. Electron-withdrawing substituents (NO_2, CN, CF_3, F, Cl) increase the corrected relative mass shift, whereas electron-donating substituents (OH, OCH_3, CH_3, NH_2) have the opposite effect.Based on the fact that Brown's σ^+ constants also correlate with the degree of dissociation in this class of compounds (data not shown), the σ^+ dependence of chemical mass shifts observed in Figure 1 allows two possibilities; one, that the observed correlations are indeed due to the electronic effects we set out to study or two, that they are due to the dissociation. This latter possibility implies that the relative ease of fragmentation may be the underlying factor determining the chemical mass shift. While we cannot demonstrate that other factors do not contribute, the fragmentation hypothesis finds strong support in simulation results obtained since this study was first formulated [21]. The dissociation correlated mass shift is readily associated with inelastic collision modification of the ejection delay. Inelastic collisions between ions and buffer gas may raise the internal energy of the ions to such an extent as to cause dissociation of the excited ion [33]. The resulting fragment ions are of lower masses than the molecular ion, and so will be unstable and immediately ejected from the ion trap. Consequently, the more fragile ions are ejected earlier than structurally stable ions. Therefore, the relative ease of fragmentation of the excited ion influences the collisional modification of the ejection delay and consequently influences the magnitude of the chemical mass shift. On the other hand, elastic collisions do not result in dissociation but can also contribute to the chemical mass shift. Chemical mass shifts due to this kind of collision are expected to be dependent on the size of the ions that vary little in the series of compounds studied.The contributions of elastic collisions to the chemical mass shift can be estimated from

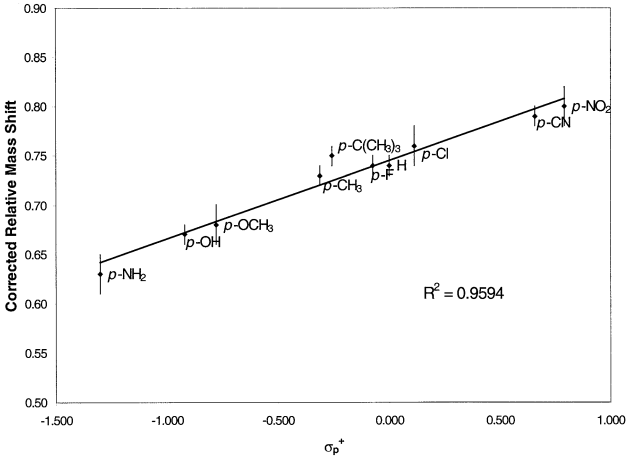

Figure 1. Correlation between corrected relative chemical mass shifts of *para*-substituted acetophenones and Brown's σ_p^+ constants.

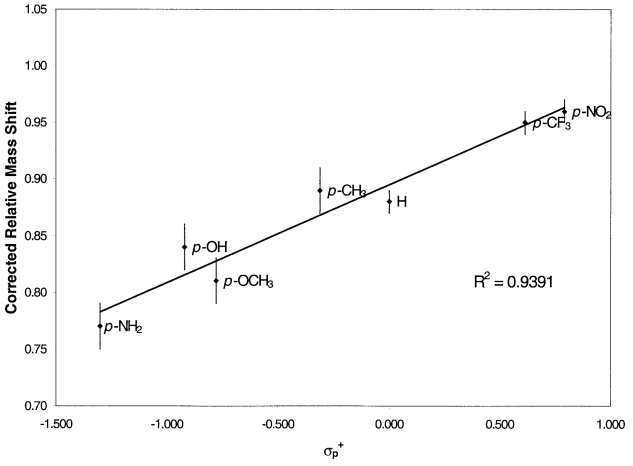

Figure 2. Correlation between corrected relative chemical mass shifts of *para*-substituted benzophenones and Brown's σ_p^+ constants.

the experimental data. To do this, the corrected relative chemical mass shifts are plotted against the ease of dissociation (% fragmentation, eq 3) of each of the acetophenones taken from literature data [34]:

$$\% \ Fragmentation = \frac{\sum Fragment\ ion\ abundance}{\sum \begin{matrix} Fragment\ ion\ abundance + \\ molecular\ ion\ abundance \end{matrix}} \quad (3)$$

By extrapolating the best-fit line, an intercept corresponding to 0% fragmentation is obtained, and this represents a very rough estimate of the chemical mass shift of an "imaginary" molecule within the acetophenone series that does not dissociate at all. The estimated non-dissociation correlated mass shift is only about 0.04 Th for the *para*-substituted acetophenones. Although these values are only rough estimates from an extrapolation method, the data do suggest that contributions from non-dissociative collisions such as elastic collisions on mass shift are small when compared to that from dissociative collisions. In conclusion, dissociative collisions appear to be the major source of the observed chemical mass shift, with non-dissociative collisions probably also contributing but to a much smaller extent. This conclusion is consistent with the results of earlier simulations [21].

Using the same experimental conditions and data manipulation procedures, mass shift results were obtained for another series of aromatic compounds, the *para*-substituted benzophenones. Results are shown in Table 1 and Figure 2. These compounds are selected for the same reasons mentioned above: Large mass shift, similar size and relatively simple fragmentation pattern. Like the acetophenones, the benzophenones also display a good linear correlation between Brown's σ^+ constant and the mass shifts, although with a slightly poorer correlation. The smaller slope may be due to the larger sizes of the benzophenones, which causes the substituent groups to have a smaller effect. In addition, the intercept obtained by extrapolation is 0.08 Th for the benzophenones, larger than that of the acetophenones, and consistent with their larger sizes.

Table 2. Chemical Mass Shifts for *meta*-Substituted Acetophenones and Benzophenones

Substituent	Brown's σ^+ Constant	Corrected relative mass shift (uncertainty)	
		Acetophenones	Benzophenones
H	0.000	0.74 (±0.02)	0.88 (±0.01)
m-NH_2	−0.160	0.51 (±0.02)	0.63 (±0.02)
m-OCH_3	0.047	0.55 (±0.02)	—
m-CH_3	−0.066	0.71 (±0.03)	0.84 (±0.02)
m-F	0.352	0.80 (±0.02)	—
m-Cl	0.399	0.80 (±0.01)	0.88 (±0.01)
m-CF_3	0.520	0.74 (±0.02)	0.90 (±0.03)
m-CN	0.562	0.77 (±0.02)	—
m-NO_2	0.674	0.85 (±0.02)	0.93 (±0.01)

In addition to the *para*-substituted compounds already discussed, *meta*-substituted acetophenones and benzophenones were studied and the experimental data are reported in Table 2. There is a general trend that the compounds with larger Brown's σ^+ constants display a larger chemical mass shift although good linear correlations are not observed. This may be because, unlike the *para*-substituted compounds, the fragmentation pathways of the *meta*-substituted compounds are much less uniform. Mass shift data for some *meta*- and *para*-substituted pyridine have also been measured (Table 3). The chemical mass shifts observed are much smaller than those for the substituted acetophenones and benzophenones. The lack of a correlation with substituent constants could be due to a variety of factors, including the more complex fragmentation patterns and the more complex substituent effects on the chemical properties of these compounds.

Conclusions

A large number of substituted aromatic compounds has been examined in a Finnigan GCQ ion trap with theoretical geometry. In two classes of *para*-substituted

Table 3. Chemical Mass Shifts for *meta*- and *para*-Substituted Pyridines

Substituent	Corrected relative mass shift (uncertainty)
H	0.03 (±0.03)
m-NH_2	0.09 (±0.02)
m-C_2H_5	0.33 (±0.02)
m-F	0.05 (±0.03)
m-CN	0.16 (±0.02)
p-OCH_3	0.24 (±0.02)
p-C_2H_5	0.35 (±0.02)
p-$C(CH_3)_3$	0.63 (±0.01)
p-CN	0.15 (±0.02)

compounds, good correlations of chemical mass shift with Brown's electrophilic constant are found. These correlations are interpreted as being the result of the correlation of σ^+ with ease of dissociation, which in turn is the result of an underlying correlation of σ^+ with ionization energy [29] and appearance energy [30] in these systems. It has long been known that the main features of the fragmentation of isolated ions having a broad range of internal energies are accounted for by energetics, with secondary effects due to fragmentation kinetics [35, 36]. This argument also justifies plotting the data of Figures 1 and 2 in a linear rather than the log fashion (i.e., log mass shift versus σ^+), as the kinetic form of the Hammett relationship would require. In fact both forms give good correlation coefficients.

Reiterating, we conclude, consistent with March's and Yost's proposals, that fragmentation is the main cause of chemical mass shifts [14, 18]. The present results also allow us to estimate that inelastic collisions make a much greater contribution than elastic collisions to chemical mass shifts. They also allow the effects of substituents to be quantified, at least in these systems. The chemical mass shifts observed in these experiments are completely removed when the instrument geometry is altered so as to cancel the effects of the negative higher order fields produced by the holes in the end-cap electrodes. Studies of chemical mass shifts for other compounds, including substituted nitrobenzenes, are currently underway.

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